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Pharmacogenetics in Psychiatry: Are We Ready for Widespread Clinical Use?

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There are high expectations about the capabilities of pharmacogenetics to tailor psychotropic treatment and "personalize" treatment. While a large number of associations, with generally small effect size, have been discovered, a "test" with widespread use and adoption is still missing. A more realistic picture, recognizing the important contribution of clinical and environmental factors toward overall clinical outcome has emerged. In this emerging view, genetic findings, if considered individually, may have limited clinical applications. Thus, in recent years, combinations of information in several genes have been used for the selection of appropriate therapeutic doses and for the prediction of agranulocytosis, hyperlipidemia, and response to antipsychotic and antidepressant medications. While these tests based on multiple genes show greater predictive ability than individual allele tests, their net impact on clinical consequence and costs is limited, thus leading to limited penetration into widespread clinical use. As one looks at other branches of medicine, there are successful examples of pharmacogenetic tests guiding treatment, and thus, it is reasonable to hope that with the incorporation of clinical and environmental information and the identification of new genes drawn from genome-wide analysis, will improve the predictive utility of these tests leading to their increased use by clinicians.

Key words: pharmacogenomics/psychotropic drugs/prediction tests/pharmacogenetics

Introduction

Pharmacogenetics, the science dedicated to the identification of genes influencing response to pharmacotherapy, had a clear breakthrough in the 1950s with the discovery that the variability of debrisoquine oxidation suggested inheritable patterns, followed by the identification of the associated genetic variants in the gene coding for the cytochrome P450 (CYP) 2D6 enzyme.[1] Since then, pharmacogenetic research has expanded to cover most fields in medicine, acquiring special importance in complex diseases, including psychiatric diseases, where pharmacotherapy is insufficient and/or expensive. Great expectations, including the hope of "tailored" or "individualized" treatment for each patient according to their genetic profile, were offered in the early days. However, a more realistic picture, recognizing the significant influence of environmental and clinical factors, has dawned over the last few years. Nevertheless, there have been several successes in other fields, and in the long run, it seems rather inevitable that some form of pharmacogenetic information will influence clinical treatment in psychiatry.

Most of the successful and clinically applicable pharmacogenetic findings relate to monogenic traits, where the substantial variability is determined by a single or a few functional variants of the same gene. In the field of cancer, pharmacogenetic tests are aimed at identifying genetic mutations causing high levels of the protein *HER2* and mutations in the *BCR-ABL* gene that stand as notable examples. Those patients with breast cancer presenting the high-level variants of HER2 are likely to respond to the drug Herceptin,[2,3] whereas chronic myeloid leukemia patients with mutated forms of the gene *BCR-ABL* associated with production of the enzyme tyrosine kinase are unlikely to respond to the drug Glivec, a tyrosine kinase blocker.[4] However, monogenic response traits are rare, and, in general, response variability can be considered a complex trait, where many genes are implicated in determining variability at pharmacokinetic and pharmacodynamic level. Given that response to psychotropic therapies is highly variable, with 30%–50% of treated patients not showing full or adequate response, it is likely that multigenic interactions play major roles in treatment efficacy. The picture is further complicated by the intervention of environmental and clinical factors and their interaction with genetic factors. In the next sections, we will review the most significant pharmacogenetic findings in the field of psychiatry and their contribution to clinical outcome in combination with environmental determinants.

How Strong Are the Genetic and Environmental Contributions?

Limited evidence coming from twin and family studies suggest that response to antipsychotic and antidepressant

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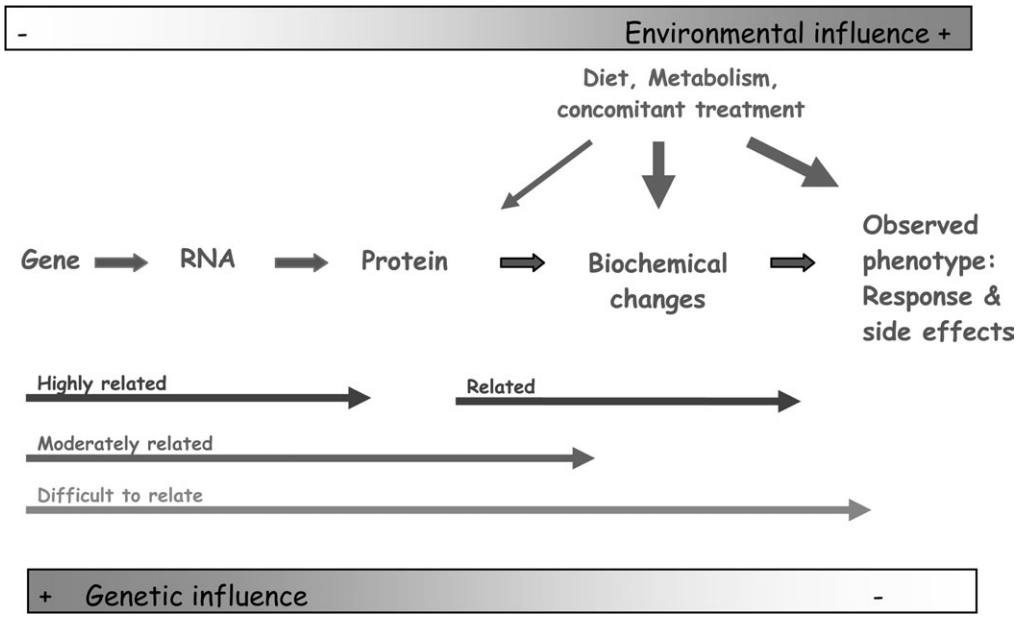

Fig. 1. Process leading to clinical outcome: Genes are expressed into RNA and transcribed into proteins that interact with psychotropic drugs. This interaction results in biochemical changes that may affect disease symptomatology. This process is influenced by environmental factors that contribute to the end (observed) phenotypes. The influence of environmental factors may be insignificant at gene level yet very influential toward the end of the sequence.

medication is a heritable trait. Studies on single pairs of monozygotic twins observed similar response to treatment with antipsychotics[5,6] and similar levels of drug-induced weight gain.[7,8] Studies on siblings and first-degree relatives observed similarities in treatment-induced tardive dyskinesia (TD), movement disorders, and response to antidepressant medications.[9–11] However, no systematic epidemiological study has been performed to separate and quantify the genetic and environmental contribution to treatment variability. In the absence of a systematic study, it is difficult to estimate the contribution of genetic and environmental factors on treatment outcome and the level of their interaction. Hypothetically, genetic and environmental factors may interact or have an independent effect during the processes leading to clinical outcome. Gene sequence variation, gene interactions, and epigenetic regulation may lead to alterations in their expression that contribute to disease etiology and treatment variability. The contribution of environmental factors to these changes varies along the process, with some influence over gene regulation (figure 1) and more significant contribution on biological and metabolic processes. The influence of environmental factors on treatment response may be insignificant at gene level yet very influential when considering the observed response and side effects.

Most of the pharmacogenetic research to date has been conducted blind to environmental influences. This may partly explain the difficulties encountered in correlating genetic variants with observed treatment variability and in replicating reported findings. Relating genetic variants with associated biological effects is relatively easy, even without considering environmental factors. However, the correlation between genetic variants and end response is less clear, especially if environmental factors are not considered in the equation. Figure 1 stresses the importance of considering environmental factors in pharmacogenetic studies, especially when investigations are conducted at the end of the sequence, close to the observed phenotypes. This figure highlights the limitations of exclusively using genetic information for the prediction of response improvement. Such approach will rarely reach high prediction levels (above 80%–90%). However, it is important to mention the advantages. Genetic information can be obtained before the start of treatment and used to select the appropriate drug according to a patient's genetic profile. Ideally, a combination of genetic and nongenetic information should be used for the selection of appropriate treatment, but genetic testing can be useful on its own as a pretreatment test.

Nongenetic Factors Influencing Treatment Response

It is difficult to define what constitutes an environmental factor, considering that drug administration and consumption can itself be considered an environmental factor. The single biggest environmental influence is compliance. While compliance may itself, in part, be genetically determined, given that the figures range in the 50%–75% mark in psychiatric disorders, the likelihood of significant findings enduring replication is limited.

Table 1. Nongenetic Factors That Influence Response to Treatment With Psychotropic Drugs

Factors	Association	Reference
Environmental		
Diet	Caffeine inhibits CYP1A2 enzymes and increases plasma levels of substrates	12
	Grapefruit is a substrate of CYP3A4 and competes with substrate drugs	12
Smoking	Cigarette smoking induces CYP1A2 and rapid clearance of drug substrates	15,16,161
Concomitant treatment	Treatment with drugs competing for same substrates reduces efficacy and increases drug-induced adverse reactions	12,19
Clinical		
BPRS	Improvement in BPRS during first 2 wk predicts longer term treatment response	36
DUP	Longer DUP predicts poor response and longer time to respond	20–26
Age of onset	Earlier age of onset predicts poor response	20,28,32
Symptom severity	Lower severity of general psychopathology, positive, and disorganized symptoms at baseline associated with lesser likelihood of response in first episode patients	20,162
	Negative symptoms predict poor response to antipsychotic treatment	27
	Severe negative symptoms predict good response to clozapine	28,28
	Higher depression scores predict lower remission and poorer response to antidepressants	25,29,30,31
	Severely depressed patients respond better to lithium	34
Rapid cycling	Bipolar patients show poorer response to long-term treatment	163
EPS	Presence of EPS predicts poorer response to neuroleptics	24,26,31,162
	Presence of EPS in previous treatment predicts good response to clozapine	32,164
ADHD	Presence of ADHD in children with bipolar disorder predicts poorer response	35
Obstetric complications	Poorer response to antipsychotic treatment	24,33
Weight gain	Predicts long-term response to clozapine	165
Demographic		
Gender	Gender differences in treatment outcome, side effect severity, and frequency	26,29,32,37–40
	Female gender show greater risk of relapse after antidepressant treatment	29
Family history	Patients with family history show poorer response to psychotropic drugs	41,166
Sociodemographic	Patients living with partners respond better to antidepressant treatment	43,44
Paternal care	Low levels of paternal care associated with poor response to antidepressants	45
Level of education	Lower levels of education predicts poor response to antidepressants	44,46
Ethnicity	Differences in dose requirements and level of response in different ethnic groups	48,167,168

Note: CYP, cytochrome P450; BPRS, Brief Psychiatric Rating Scale; DUP, duration of untreated psychosis; EPS, extrapyramidal side effects; ADHD, attention deficit/hyperactivity disorder.

The effects of compliance on response are self-evident and have been dealt extensively elsewhere so will not be dealt further here. However, several external environmental factors such as diet, substance abuse, smoking habits, and concomitant treatment have a significant effect on therapeutic dose requirement and subsequent response (table 1). Caffeine and grapefruit inhibit CYP1A2 and CYP3A4 enzymes, respectively, for which they compete with drug substrates such as clozapine and risperidone.[12] Substance abuse is associated with poorer response and higher relapse rates.[13,14] Cigarette smoking induces CYP activity and accelerates the metabolism of substrate drugs.[15,16] This has a direct effect on drug dose requirements, nonsmokers requiring lower doses of drugs than smokers.[17] Concomitant treatment may have similar effects to smoking, with CYPs being inhibited or stimulated by certain drugs.[18] Although newer antipsychotics do not significantly influence CYP metabolism, neuroleptics and antidepressant medications are known to reduce metabolic activity by competing for the same enzymes.[12] Anticonvulsant drugs have the opposite effect, inducing the activity of CYP1A2 and increasing the metabolic rate of clozapine, olanzapine, and risperidone among others.[19] Very little is known about other internal environmental factors (eg, drug interactions at receptor level) and their effect on treatment efficacy. Internal pharmacodynamic interactions occur when drugs with similar pharmacological properties are used and are competing for the same brain receptors, and it is often the result of concomitant treatment.

Clinical factors have a clear influence on treatment variability. Duration of untreated psychosis has been associated with poorer prognosis in several studies.[20–26] Symptoms severity and type are associated with response fluctuation.[27–30] Severely depressed patients show poor response to antidepressants but good response to lithium.[31] An early age of onset and obstetric complications predict poor response to antipsychotic treatment.[20,24,28,32,33] Rapid cycling and presence of attention deficit/hyperactivity disorder (ADHD) in bipolar patients are correlated with poorer

response to antidepressants.[34,35] Presence of weight gain and extrapyramidal side effects (EPS) in previous treatments predict good response to clozapine.[36]

Several demographic factors have been described with an influential effect on response. Gender differences have been detected in relation to the level of response[26,29,32,37–40] although the direction of the relation varied in different studies. Patients with family history of mental disorders show poorer response to antidepressant and antipsychotic drugs.[41,42] Sociodemographic factors (living with partners, educational level, paternal care) have a clear influence in the response to antidepressant medications.[43–46] Finally, ethnic differences have been observed in relation to dose requirements and level of response[47]; mixed and black South Africans responded better than whites to antipsychotic treatment.[48] However, these differences may be a direct reflection of genetic differences, cultural habits, and diet variation between population groups.

Undoubtedly, some of the influencing factors considered here may be directly correlated with genetic causes (eg, symptom severity). However, it is evident that nongenetic factors play an important role in response fluctuations. Unfortunately, most pharmacogenetic studies to date have failed to account for nongenetic factors, and this may explain the difficulties of finding clear genetic associations that can be replicated in different clinical cohorts.[49–51] Additionally, gene-environment interactions and their influence on treatment response remain to be investigated, and only recently pharmacogenetic studies have started to include them in the experimental design.

Genetic Factors Influencing Treatment Response

Most pharmacogenetic studies in the last 2 decades have used candidate gene approaches, selecting genes to be investigated from current knowledge, for the identification of response related genes. Candidate genes involved in pharmacokinetic and pharmacodynamic processes have been thoroughly investigated, and recent investigations have expanded to genes involved in neuronal plasticity, transport, and metabolism. The following sections will summarize significant gene-response associations with a focus on positive findings. We have not attempted to make an exhaustive review of the literature, which can be found elsewhere.[19,52,53] From a clinical point of view, the critical issue is not just finding a statistical association but the effect size of that association. Thus, where possible, we have tried to point out not only whether an association exists but also the effect size (and hence in some ways the practical utility) of the findings so far.

Pharmacokinetic Factors

Pharmacogenetic investigations of pharmacokinetic factors have produced the clearest associations with treatment response variability. Possibly because there are several monogenetic traits controlling pharmacokinetic processes (eg, drug metabolization). Additionally, environmental interactions with pharmacokinetic factors (eg, diet, smoking habits, caffeine intake) are clearer than with pharmacodynamic factors, and this facilitates the identification of related genes.

CYP Genes

Genes encoding for enzymes involved in phase 1 (mainly CYP enzymes) are known to contain functional polymorphisms that significantly alter their normal metabolic rate. Relatively common polymorphisms in genes coding for CYP enzymes with a significant effect on their metabolic rate, rendering the enzyme slow or inactive (PM) or ultrarapid (UM), are well characterized.[54,55] In particular, CYP2D6, an abundant hepatic enzyme involved in the biotransformation and elimination of many antidepressant and antipsychotic medications, has been thoroughly investigated and associated with propensity to develop toxic reactions. Individuals presenting CYP2D6 PM variants are more likely to develop EPS, TD, and weight gain (range of available odds ratios [ORs]: 1.6–4.4)[56–62] (table 2). Studies by Kirchheiner et al[53] showed that CYP2D6 and CYP2C19 metabolic rates may have an important influence in the required therapeutic doses of antidepressants and antipsychotics substrates for these enzymes. This is a clear example of the potential clinical use of pharmacogenetic information, especially when combined with relevant environmental and clinical information. Interestingly, the distribution of CYP2D6 variants varies geographically, with PM constituting 7%–10% of Caucasians and only 1%–2% of Asians, whereas black African populations show significant geographical variations. Geographical variation is also observed in the distribution of other CYPs functional variants (eg, CYP2C19), contributing to the hypothesis that metabolic polymorphisms account for a significant proportion of variability in response to medications.

Similar functional polymorphisms have been observed in the genes coding for CYP1A2, CYP2C9, CYP2C19, and CYP3A4 enzymes. Wheras CYP2C19 may be clinically relevant for the metabolism of antidepressants, CYP1A2 and CYP3A4 are the main metabolic pathways of most commonly used antipsychotics, including olanzapine, risperidone, aripiprazol, and clozapine.[19] Slow CYP1A2 variants have been associated with increased risk of drug-induced side effects[58,63,64] with a reported odds ratio of 1.9.[58] It is known that smoking can induce CYP1A2 activity, especially of the variants containing the *1C and *1D alleles.[65] This example of a gene × environment interaction may have clinical significance as individuals with CYP1A2 ultrarapid phenotypes are known to experience delay or lack of response to treatment with

Table 2. Significant Associations of Genes Involved in Pharmacokinetics, Pharmacodynamics, and Neuronal Processes With Response to Psychotropic Medications

Gene	Reported Association	OR	References
ADRA1A	Associated with antipsychotic-induced side effects	0.49–0.7	105
ADRA2A	Associated with antipsychotic-induced weight gain	2.5–4.2	106,107
BDNF	Associated with antipsychotic response	2.6	110
	Associated with orofacial tardive dyskinesia and EPS	n/a	112,113
	Associated with remission after antidepressant treatment	2.95	111
COMT	Associated with working memory improvement and antipsychotic response	3.9	115–118
	Associated with risk of tardive dyskinesia	0.24–0.63	57,114
CYP1A2	Associated with antipsychotic-induced side effects	1.9	58,63,64
	Associated with delay or lack in response to antipsychotic treatment	n/a	66,67
CYP2D6	Associated with drug-induced side effects and dose requirements	1.6–4.4	58–61,169,170
	Associated with antipsychotic-induced weight gain	n/a	62
DAT1	Associated with response to ADHD medication	1.7–2.6	159
D2	Associated with antipsychotic response	2.6–6.7	56,79–84
	Associated with antipsychotic-induced tardive dyskinesia	1.3–2.1	57,69
	Associated with neuroleptic malignant syndrome	2.3–10.5	171,172
D3	Associated with level of response and improvement in positive symptoms with antipsychotics	1.4-4.7	72–74,76–78,85
	Associated with antipsychotic-induced tardive dyskinesia	1.17–3.15	70,71
D4	Associated with antipsychotic response	2.63	173–175
GABA	Associated with drug-induced tardive dyskinesia	1.38–2.38	104
GNB 3	Associated with antipsychotic treatment	n/a	134
	Associated with antipsychotic-induced weight gain	n/a	137
GRM3	Associated with negative after treatment	n/a	103
GSTM1	Associated with tardive dyskinesia	1.7	68
5-HT_{1A}	Improvement in negative symptoms	n/a	68
5-HT_{2A}	Response to antipsychotic treatment	1.6–5.7	86–88
	Response to antidepressant treatment	n/a	89,90
	Associated with antipsychotic-induced tardive dyskinesia	1.5–5.3	92
5-HT_{2C}	Associated with antipsychotic response	6.4	73,101,176
	Associated with antipsychotic-induced weight gain	n/a	95,96
	Associated with antipsychotic-induced EPS and tardive dyskinesia	2.1–3.2	176,178
5-HT_6	Associated with clozapine and risperidone response	n/a	49,179
5-HTT	Associated with antidepressant response	0.53	97,98
	Associated with antidepressant side-effects	0.67	99
	Associated with antipsychotic response	2.61	100,101
Leptin	Associated with antipsychotic induced weight gain	3.68	96,128
MDR1	Associated with antipsychotic treatment	n/a	119,121,123
	Associated with response to antidepressant medications	7	120,122
MnSOD	Associated with drug-induced tardive dyskinesia	0.37–0.49	57
NET	Associated with antidepressant response	2.10	138
NOS3	Associated with tardive dyskinesia	0.65	129
NQ01	Associated with tardive dyskinesia	2.2	130,131
NRG1	Associated with antipsychotic response	3.2	132
RGS2	Associated with antipsychotic-induced side-effects	3.44	125,126
RGS4	Association with antipsychotic response	n/a	124,127
SNAP25	Associated with weight gain	n/a	133,135
TNF-α	Associated with antipsychotic response	n/a	139
	Associated with risk of agranulocytosis	n/a	

Note: *OR = odds ratio (average range of odds ratios); BDNF = brain-derived neurotrophic factor; EPS = extrapyramidal side effects; COMT = catechol-*O*-methyltransferase; n/a = odds ratios values not available; TNF-α = tumor necrosis factor alpha. ORs are given when mentioned in the original article of when the reported data allow for their calculation.

clozapine, a CYP1A2 substrate.[66,67] Few reports have investigated CYP3A4, CYP2C9, and CYP2C19 functional variants and their influence on clinical outcome, with only some reference to the influence of CYP2C19 variants on therapeutic doses of antidepressants.[53]

Phase 2 Enzymes

Less information is available on phase 2 enzymes (*N*-acetyltransferases, UDP-glucuronosyltransferases, and glutathione-*S*-transferases), although functional polymorphisms have been described in the genes coding

for these enzymes. A recent report by de Leon et al[68] associated the null variant (absence) of the gene coding for a glutathione-*S*-transferase enzyme (GSTM1) with drug-induced TD, probably due to accumulation of metabolites substrates of the missing enzyme.

As described in the previous section, environmental factors may contribute to alterations in CYPs metabolic rates, significantly slowing or increasing drug metabolism. Nevertheless, the CYP findings reported in this section are, to date, the clearest associations demonstrated between genetic variants and response phenotypes (including blood levels and drug-induced side effects).

Pharmacodynamic Factors

Receptors and transporters involved in the pharmacodynamic processes are obvious selections in studies using candidate gene approaches for their implication in disease pathophysiology and treatment mechanisms. Pharmacogenetic studies have confirmed the importance of several brain neurotransmitter systems in mediating treatment efficacy or side effects. The following section will summarize the most significant findings (listed in table 2); not every single study on an issue is listed so this table should be considered representative but not complete.

Dopaminergic System

Dopaminergic blockade is a common characteristic of most antipsychotic medications and partly mediates their antipsychotic activity. Pharmacogenetic studies confirm this hypothesis, and genetic variants in dopamine receptors have been found associated with treatment response. The most significant results correlate dopamine 2 (D2) and dopamine 3 (D3) receptor variants with response improvement. A *D2* variant, *Taq* A1, has been associated with risk of TD, with the A2 allele conferring a higher risk (odds ratios: 1.3–2.1).[57,69] The significance of this association is not yet clear as the A1 allele is associated with lower D2 levels and would be expected to increase TD risk.[69] Similarly, a D3 9Gly variant that confers higher binding affinity has been reported to increase the risk of TD.[70,71] Several studies have associated *D2* and *D3* polymorphisms with levels of response to antipsychotic treatment[72–85] (see table 2). In general, the alleles associated with lower expression indicated poorer levels of response. In spite of the reports that have failed to replicate the significance of these findings, these studies constitute evidence of the importance of the dopaminergic receptors and transporter in mediating antipsychotic activity.

Serotonergic System

Second-generation antipsychotics display high affinities for serotonin (5-HT) receptors that are hypothesized to mediate, at least partially, their antipsychotic activity. In addition, antidepressant medications are thought to regulate monoaminergic transmission via the serotonergic pathway. In support of these hypotheses, several polymorphic variants in 5-HT2A and 5-HT2C receptors have been associated with response to treatment with clozapine, although these findings have not been universally replicated. A *5-HT2A* 102-T/C silent polymorphism and a -1438-G/A reporter variant have been associated with response to the antipsychotics clozapine and risperidone and with the antidepressant mirtazapine.[86–90] The -1438-G allele, in complete linkage disequilibrium with the 102-C allele, is associated with lower expression of the 5-HT2A receptor protein and with poorer response to treatment in Caucasians.[86,91] Targeting of serotonin receptors may also be associated with adverse reactions. It has been hypothesized that serotonin inhibition of dopamine function contributes to the development of EPS. Several studies showing significant associations between 5-HT2A and 5-HT2C receptor variants and TD, EPS provide evidence in support of this hypothesis. Although a number of studies failed to replicate these findings, the associations are clearer when the patients' age, an important factor in the development of side effects, is taken in consideration.[92–94] This reinforces the need for conducting studies combining genetic, clinical, and environmental information. 5-HT2C receptor variants have also been associated to drug-induced weight gain, reflecting the involvement of the serotonin system in feeding behavior.[95,96] The serotonin transporter (5-HTT) regulates serotonin function by reuptaking free synaptic serotonin and is a target for antidepressant medications. Numerous studies have associated a functional polymorphic variant in the promoter region of the gene, LPR, with response to selective serotonin reuptake inhibitors antidepressants. Most studies in Caucasian patients correlate the short LPR allele, associated with lower expression of the transporter protein, with poor response to antidepressants, as confirmed by recent meta-analyses.[97,98] Surprisingly, a large study on patients treated with citalopram failed to replicate this finding,[89] although an association between this polymorphism and citalopram-induced side effects was reported.[99] This polymorphisms has also been associated with response to the antipsychotics, risperidone and clozapine, both with strong affinities for serotonin receptors.[100,101]

Drug-Targeted Neurotransmitter Systems

The multitarget profile of most psychotropic drugs suggests that, in addition to the serotonergic and dopaminergic systems, other systems play a role in determining clinical outcome. Candidate gene studies may help to validate other drug-targeted receptors as therapeutic targets by identifying variants in their coding genes correlated with treatment response.

The targeting of glutamatergic receptors is suggested to have antipsychotic properties,[102] and a report of association between metabotropic glutamate receptor 3 gene (GRM3) polymorphisms and antipsychotic response supports this hypothesis.[103] Additionally, a genome-wide association study revealed that genes in the γ-aminobutyric acid–mediated (GABA) signaling pathway were related to risk of developing TD.[104] Targeting of adrenergic receptors has been associated with increased adipogenesis and weight gain. Not surprisingly, recent reports associate polymorphisms in these receptors with drug-induced weight gain and related side effects.[105–107]

Developmental and Regulatory Genes

Genes implicated in developmental, regulatory, and plasticity processes hypothesized to contribute to the pathophysiology of mental disorders may interact with drug-targeted systems and contribute to response determination. A number of genes falling in this category have been associated with treatment variability.

Loss of the brain-derived neurotrophic factor (BDNF) from the hippocampus contributes to vulnerability for depression, whereas BDNF upregulation mediates antidepressant efficacy.[108,109] Several recent reports have linked polymorphisms in the *BDNF* gene with response to antidepressant and antipsychotic drugs (OR: 2.6–2.95, respectively), and with drug-induced side effects.[110–113] The catechol-*O*-methyltransferase (COMT) catalyses the degradation of dopamine and other catecholamines and regulates their availability. The *COMT* gene contains a polymorphic Val108/158Met variant of functional activity. The Met allele is associated with better response to antipsychotics (OR: 3.9) and with fewer side effects (OR: 0.24–0.63),[57,114–118] in what constitutes a surprizing finding because the Met variant is associated with lower enzyme activity and therefore with dopamine accumulation. Multidrug resistance 1 (MDR1, also known as ABCB1) encodes a blood-brain barrier transporter, P-glycoprotein, that regulates the passage of substances through the barrier. Several polymorphisms in the *MDR1* gene of yet unknown functionality have been associated with response to antipsychotic and antidepressant medications with one study showing an odds ratio of 7.[68,119–123] Two regulator proteins of G signaling pathways, RGS2 and RGS4, have recently been linked to antipsychotic response variability and drug-induced adverse reactions,[124–127] reflecting the importance of regulatory processes in determining clinical response. The gene coding for Leptin, a hormone that regulates food intake, contains a -2548-A/G polymorphism of yet unknown function that is associated with drug-induced weight gain.[96,128] Several proteins involved in oxidative stress regulation processes, NOS4, NQ01, and MnSOD, have been associated with drug-induced TD.[57,129–131] Unclear results have been obtained in studies of a number of genes involved in developmental and regulatory processes, including neuregulin (NRG1), involved in cell-cell interactions; protein β3 subunit (GNB3), involved in the regulation of second messenger cascades; tumor necrosis factor alpha, involved in cytotoxicity and neural transmission; the norepinephrine transporter gene, involved in the reuptake of norepinephinre; and the synaptosomal-associated protein 25 kD that plays an important role in the regulation of neurotransmitter release.[132–139] However, the biological importance of these genes warrants further investigation.

It is important to stress that most of the findings reported in this section have not been universally replicated ([19,53] for reviews of nonsignificant studies). A number of negative findings may be caused by differences in methodologies and clinical characteristics, and protocols trying to standardize pharmacogenetic methodologies have been attempted.[140–142] However, the likelihood of false positives in gene association studies is very high, and findings should be considered with caution unless replicated.

Dopaminergic and serotonergic findings have been not only the most consistently replicated but also the most widely studied. Nevertheless, these findings confirm the importance of the dopaminergic and serotonergic systems in antipsychotic and antidepressant activity. Lack of clearly significant findings in other neurotransmitter receptors may be a result of the lesser number of studies performed on them, in particular, on the glutamatergic system. However, it may also indicate a lesser contribution to the activity of currently available drugs, as would be expected by their bias toward dopamine and serotonin receptor binding. Thus, the current pharmacogenetic findings are a reflection of the pharmacological profiles of currently available drugs and do not constitute an evaluation on the therapeutic potential of other targets such as glutamateric receptors.

Genetic × Environmental Interactions Influencing Response to Psychotropic Drugs

Very limited information is available on the interactions between clinical, environmental, and genetic factors and their influence in treatment variability. Most published pharmacogenetic studies lack information on clinical and environmental factors and focus only on genetic influences. In addition, separating the genetic, clinical, and environmental contribution to treatment variability is proving a difficult task, accentuated by the lack of epidemiological family and twin studies to quantify their relative contribution.

The best examples of genetic × environmental interactions are found in the area of pharmacokinetics. This may be because environmental influences are relatively easily determined in comparison to internal and external environmental influences on pharmacodynamic processes. In

many cases, the interactions are with monogenic traits (eg, single functional variants in CYP genes), which facilitates their identification. As reviewed in the section on nongenetic factors, there are clinical (eg, symptomatology type and severity), demographic (eg, gender, ethnicity, age), and environmental (eg, diet, smoking habits, substance abuse) inducers and inhibitors that may affect clinical outcome depending on their influence on drug-metabolizing rates.[61,68,121]

Some studies have investigated possible interactions between clinical and demographic factors and genes involved in pharmacodynamic processes, with a few significant results. As mentioned in the previous section, polymorphic variants in the genes coding for serotonin receptors are reportedly associated with antipsychotic response, drug-induced weight gain, and TD.[49,50,71,92] Interestingly, the findings are more significant when clinical (eg, dose and duration of treatment) and demographic (eg, age, ethnicity) variables are taken into consideration.[51] However, no significant studies have been reported investigating environmental interactions with genes involved in pharmacodynamic processes. Internal and external environmental factors influencing pharmacodynamic processes (eg, competition for targeted receptors, environmental induction of receptor protein expression) are complex and difficult to measure. However, it is clear that the application of this knowledge to pharmacogenetic studies will improve the chances of identifying the factors determining outcome variability.

Pharmacogenetic Prediction Tests in Psychiatry: If and When?

The ultimate goal of pharmacogenetic research is the clinical application of genetic information for optimizing treatment for each patient. However, most of the current pharmacogenetic findings (barring drug-metabolizing polymorphisms) have a limited predictive value, with odds ratios for individual alleles or genotypes of 1.5–2 on average. Although the individual clinical value of such findings is limited, attempts have been made to combine genetic information in the development of clinically useful genetic prediction tests. It is important to note that, from an ethical point of view, different considerations apply to genetic tests designed to identify individuals prone to develop a disease and tests designed to identify individuals likely to respond to a specific treatment. For a diagnostic test, a very high level of predictive value is required because it entails providing someone with risk information for which no interventions may be available. A pharmacogenetic test however is a clinical decision–support tool, where useful information is provided to the clinician on the likelihood of success of a particular medication or intervention—and thus, a lesser predictive value may suffice. Further, pharmacogenetic tests have several advantages over other available prediction tests (eg, blood levels, clinical observations during early treatment). A genetic test needs to be performed just once, and, because genetic information does not change, the information obtained remains valid during a lifetime. Additionally, a genetic test does not require drug intake and therefore can be used to select an appropriate drug (eg, non-CYP2D6 substrates for individuals with slow CYP2D6 variants) even before the start of the treatment. Finally, because pharmacogenetic tests are used for different purposes—their utility also depends on the cost and consequence of the outcome they predict. A test with even a slight positive predictive value that can prevent death may be of very high clinical utility, whereas a test with the same predictive value to prevent dry mouth as a side effect will go largely unused.

Currently Available Genetic Tests in Psychiatry

Several psychiatric pharmacogenetic tests are currently available, including tests for the determination of metabolic status, risk of agranulocytosis and metabolic syndrome, and selection of beneficial medications.

Genetic tests for the determination of the drug metabolism status of the patient were the first to be developed. Relatively easy and economic methods for the determination of CYP poor and ultrarapid metabolizers have been described in several reports.[143–145] More sophisticated kits for the genotyping of a variable number of functional CYP variables are commercialized by a number of companies. An array incorporating oligonucleotides for the recognition of most common polymorphisms described in CYP2D6 and CYP2C19 genes (AmpliChip CYP450) has been recently approved for clinical use by the American Food and Drug Administration agency.[146] These tests are applicable not only in psychiatry but also in all areas of medicine using CYP substrates and have been included in the clinical trials of new drugs, including the cancer treatment tamoxifen.[147] Surprisingly, the use of CYP genotyping in clinical settings is rare, and this may be due to several causes. Lack of knowledge, lack of genotyping facilities, difficulties of interpretation of results, economical costs of genotyping arrays are some of the reasons hampering the clinical implementation of CYP genotyping. It is hoped that lowering genotyping costs and commercialization of cheaper and simpler-to-interpret genotyping kits will greatly facilitate the routine genotypic characterization of patients' metabolic status. It has been estimated, perhaps optimistically, that pretreatment determination of the patients metabolic status may increase the efficacy of pharmacotherapy in 10%–15% of cases and result in a 15%–20% reduction of drug-induced adverse reactions.[148] However, there is no hard evidence yet supporting (or contradicting) these efficiency values.

Genetic variants in human leukocyte antigens have been associated with the risk of drug-induced agranuloctysis.[149] Using this information, a biopharma company (Clinical Data) offers a genetic test for the determination of high (1.5%) or low (0.5%) risk of developing agranulocytosis.[150,151] While this test will not obviate the need for routine blood cell monitoring, it may help in the selection of appropriate treatment. While the test represents a step in the right direction, because it does not meaningfully impact clinical choice, its uptake has been limited. Knowing that the risk increases from the average 1 to 1.5% suggests a greater alert, but in 98.5% of the cases, the patient will still not encounter this effect—and because there is mandatory monitoring in place anyway, no different strategy is advised. Similarly, while there is some comfort in knowing that the lower risk is 0.5% (a 50% reduction of risk from the standard 1%), it still does not obviate the need for regular and frequent monitoring. Thus, this test is a good example of a clear pharmacogenetic association that does indeed make a valuable prediction, but the prediction does not significantly impact clinical choices in routine patients.

A high prevalence of metabolic syndrome (hyperlipidemia, diabetes, obesity, and hypertension) has been observed in patients undergoing antipsychotic treatment,[152] and a number of influencing genes have been described. A recent study describes an array containing probes to identify genetic variants conferring risk of hyperlipidemia.[153] However, the clinical utility of this array is still under investigation.

In our laboratory, we attempted to combine genetic information for the prediction of response to the antipsychotic clozapine. A combination of polymorphisms in 4 genes resulted in a prediction level of 76%.[101] However, these values were only applicable to British Caucasian patients who had been on long-term treatment and were not replicated in a German clinical cohort on shorter treatment.[154] This illustrates how a pharmacogenetic tests needs to be validated in different clinical settings and population backgrounds before wider implementation, thus limiting their chances of successful implementation.[155] An improved prediction algorithm for clozapine response is currently being tested on the British population, and similar tests for the prediction of response to treatment with the antipsychotics olanzapine and risperidone are under development.

The pharmacological profile of antidepressant medication indicates strong targeting of the serotonergic system, and several clear associations with serotonergic variants have been described.[53,98,156] Although no specific prediction test for response to antidepressant medications has been described, a medical institution is offering genetic testing for antidepressant-associated adverse reactions.[157]

Finally, several reports have described the genetic influence on the response to pharmacotherapy in Alzheimer disease and ADHD.[158,159] However, no related pharmacogenetic tests have been described.

Conclusions

Pharmacogenetic research and candidate gene approaches have succeeded in the identification of several genetic factors influencing treatment response. In particular, associations between variants in CYP enzymes, dopamine, and serotonin genes have been repeatedly associated with different response improvement and treatment-associated side effects. However, their genetic effect is relatively small, as shown by the modest odds ratios (1.5–2.5, on average). The picture is further complicated by the well-documented contribution of environmental, clinical, and demographic factors, which remain largely unstudied. Nevertheless, characterization of drug metabolizing polymorphisms has been shown to be useful to identify individuals who are poor drug metabolizers and at risk of developing adverse reactions, and several genotyping methods are already being used in clinical trials and settings. Tests combining information in several genes for the prediction of response to antipsychotics and antidepressant medications, agranulocytosis, and hyperlipidemia have also been developed, although not yet widely used in clinical settings.

However, candidate gene approaches are limited by the current knowledge of the mechanism of action of antipsychotics. Different strategies are required for the identification of novel factors related to treatment. The study of sequence variants along the genome (genomics), of gene and protein expression fluctuations (transcriptomics and proteomics), and of nongenetic inherited factors (epigenetics) are relatively new strategies that have been made possible by development of high-throughput techniques in recent years. Their main advantage over candidate gene approaches is their capability to interrogate the entire genome and proteome without requiring previous hypothesis and thus discover novel factors that intervene during treatment. In particular, the study of epigenetic events (eg, DNA methylation, histone modification, and chromatin remodeling), clearly influenced by environmental factors, promise to discern the contribution of gene × environmental factors.[160]

In summary, significant pharmacogenetic findings have been achieved in psychiatry, some of which have been translated into genetic prediction tests. The incorporation of environmental and clinical information in pharmacogenetic studies will facilitate the identification of response determinants, leading to an improvement of response prediction and treatment selection. We hope that this, in combination with better information of their applications and utilities to clinicians, will lead to a more widespread use of pharmacogenetic tests in the near future.

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